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EXAMINER	
GALVEZ, JAMES JASON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,400	WILLIAMS ET AL.	
	Examiner	Art Unit	
	J. Jason Galvez	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32 and 37-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32 and 37-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *seq. alignments*.

Response to Amendment

The amendment filed 2/15/2005 has been made of record. Claims 31-32 and 37-55 are pending. Claims 31-32 have been amended. Claims 37-55 have been added and are drawn to the elected invention. Accordingly, claims 31-32 and 37-55 are considered for examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Priority

Applicant states that it is believed that the applications 07/309,322, and 07/151,414, in the priority claim, support the instant invention. However, Applicant has provided no support for this assertion. It clearly states in the previous office action, "If Applicant disagrees with the Examiner's assessment and factual determination as stated above, it is Applicant's responsibility to provide the serial no. and specific page(s) of any patent application filed prior to 01/31/1991 that specifically supports particular claim limitations for each and every claim limitation in all of the pending claims that Applicant considers to have been in possession of and fully enabled for prior to 01/31/1991." Therefore, as previously set forth, the priority date of the instant invention is 01/31/1991.

Claim Rejections/Objections Withdrawn

Claim Objections

Objection to claims 3, 16, 17, and 28 have been withdrawn as a result of cancellation of the claims and due to the claims being drawn to non-elected subject

matter. However, Applicant again is advised on the improper referencing of sequences in the claims (see claim 43, discussed below).

Claim Rejections- 35 U.S.C. § 112

The rejection of claim 31 under 35 U.S.C. 112, first paragraph, as lacking enablement commensurate in scope with the claim and written description for a method of selecting molecules capable of inhibiting the binding between all polypeptides and targeted phosphorylated polypeptides is withdrawn upon further consideration and as a result of Applicant's amendments.

Claim Rejections- 35 U.S.C. § 103

In response to Applicant's amendments, rejection of claim 31 under 35 U.S.C. 103(a) as being obvious over Kazlauskas *et al.* in view of Sporn *et al.* is withdrawn.

Upon further consideration and in response to Applicant's amendments and arguments, rejection of claim 31 under 35 U.S.C. 103(a) as being obvious over Murray *et al.* and Sporn *et al.* is withdrawn.

Claim Rejections/Objections Maintained/New Grounds

Claim Objections

Claims 42-43 are objected to because of the following informalities: claim 42 recites, "wherein said said PDGF" and claim 43 refers to sequences in table 2 and 3 instead of referring to SEQ ID NOs. Proper referral to a sequence in the claims requires

referencing SEQ ID NOs. For the purpose of examination, Table 2 was examined as SEQ ID NO: 4 and Table 3 was examined as SEQ ID NO: 2. Appropriate correction is required.

Claim Rejections- 35 U.S.C. § 112

The rejection of claim 31 as being indefinite for omitting essential steps, such as a correlation step, under 35 U.S.C. 112, 2nd paragraph is maintained for reasons of record in the office action of 15 November 2004 and is also applied to claims 32 and 37-55.

Applicant argues that the claims have been amended to recite an "inhibitory effect", which renders the claims clearly defined. Page 47 (lines 11-15) and page 60 (6-29) are also cited by Applicant to support that the claim is not indefinite.

The amendment to the claims whereby "inhibitory effect" is added does not constitute a correlation step. A correlation step defines a quantifiable relationship that is indicative of obtaining an effect. Neither the amendment nor the specific pages recited by Applicant constitute a correlation step. For example, claim 42 recites potential outcome measures, again Applicant has only performed the assay in regards to looking at binding and PI-3 kinase activity, however it is not known based on the disclosure or the prior art what effect would demonstrate a result using the instant method. Does pH, or any other measure recited, go up or down?

Amended claims 31-32 and new claims 37-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of selecting molecules capable of inhibiting the binding between PDGF receptors and PI-3 kinase by measuring binding between PDGF receptors and PI-3 kinase or by measuring PI-3 kinase activity, does not reasonably provide enablement for selecting molecules capable of inhibiting the binding between PDGF receptors and PI-3 kinase by an unspecified "analysis" or by measuring "proliferation rate, level of phosphotidylinositol turnover, level of protein kinase C, level of protein kinase A, cAMP level, amount of activation of phospholipase A_2, cellular calcium concentration, and intracellular pH". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant has disclosed the claimed invention, a method of screening for molecules that can inhibit the binding between PDGF receptors and PI-3 kinase, by demonstrating that in the presence of molecules capable of inhibiting the binding between the two there is an interruption of binding between PDGF receptors and PI-3 kinase and a decrease in PI-3 kinase activity. However, Applicant has recited other potential measures ranging from an unspecified "analysis" to measuring intracellular pH.

Although "analysis", as recited in the instant method, was originally rejected as not meeting the written description requirements under 35 U.S.C. § 112, 1st paragraph, the arguments Applicant has set forth regarding this rejection are addressed for the purpose of compact prosecution, along with rationale for the current rejection. Applicant

argues that the specification provides support for the broad recitation of using the claimed method whereby "analysis" of samples takes place. To support Applicant's position, the specification is cited at pp. 11, 46-47, and 60. Finally, Applicant asserts that the method is clearly defined and requests that the rejection be withdrawn.

The pages in the specification cited by Applicant do not support the broad recitation of "analysis". Page 11 (lines 18-29), pages 46 and 47 (lines 35-38 and 1-16 respectively), and page 60 (lines 27-30) do not discuss any particular type of "analysis", other than inhibiting binding of an "85 kD protein". Applicant has only shown the method in response to the ability to potentially identify compounds or molecules by measuring the interruption of binding between a PDGF receptor and an 85 kD protein and by measuring PI-3 kinase activity (see for example Fig. 4a and 4b, respectively). Since Applicant has only provided support for the instant method of screening by looking at binding and PI-3 kinase activity, a person of ordinary skill in the art would not know how to use the invention commensurate in scope with the claims because "analysis" encompasses a plethora of outcome measures, such as DNA laddering or redox state of mitochondrial proteins, that would not be indicative of an effect in the instant case. The outcome measures further comprise measures that are not specific to inhibiting binding between PDGF and PI-3 kinase. Therefore, it would not be unquestionably known whether the unknown screened was affecting PDGF receptor binding to PI-3 kinase or altering some other mechanism in cell that gave the same effect.

The recited outcome measures in claim 42 are diverse in nature and do not represent specific events to the inhibition of the binding between PDGF receptors and PI-3 kinase. For example, molecules, i.e. unknowns screened in the instant method, that interact with ion channels can affect cellular Ca^{2+} concentration. The issue is whether or not the recited outcome measures are specific to molecules that inhibit the binding between PDGF receptors and PI-3 kinase. As previously noted, when an unknown is screened it would not be clear if this effect would be a result of inhibiting the binding between PDGF receptors and PI-3 kinase or some other effect of the unknown. Without further guidance in the disclosure or the prior art, a person of ordinary skill in the art would not know how to use the invention as claimed. If Applicant believes these outcome measures are routine and would be well known to a person of ordinary skill in the art to be useful in the instant method, evidence in required.

For the reasons set forth, without further guidance a person of ordinary skill in the art would not be able to practice the invention commensurate in scope with the claims without undue experimentation.

New claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. The claim is drawn to methods of using "homologous" peptides. However, it is unclear what is and what is not a "homologous" peptide. On page 23 of the specification, Applicant refers to parameters of homology, such as 80% homologous, using the term ordinarily, which does not impart a definition upon "homologous" peptides. As such, a person of ordinary skill in the art would not be

able ascertain the metes and bounds of the claim in order to avoid infringing upon the method as claimed.

Claim Rejections- 35 U.S.C. § 103

Amended claims 31-32 and new claims 37-44 and 46-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kazlauskas *et al.* (Cell, Vol 58: pp. 1121-1133 [1989]) in view of Sporn *et al.* (The Journal of Clinical Investigations, Vol. 78: pp. 329-332 [1986]) and further in view of Matsui *et al.* (Science 1989, Vol. 243(4892): pp. 800-804) and Gronwald *et al.* (Proc Natl Acad Sci U S A 1988, Vol. 85(10): pp. 3435-3439). Kazlauskas *et al.* teaches that autophosphorylation of PDGF receptors results in receptor activation and cellular changes, such as association of cellular polypeptides with the receptor (p. 1129: column 2, paragraph 2) and PI-3 kinase activity (p. 1127: Figure 8). The methods used by Kazlauskas *et al.* could be used as a method for screening compounds that inhibit the binding of two polypeptides, which is phosphorylation dependent, with at least one of the polypeptides being autophosphorylated PDGF receptors. The core methods used by Kazlauskas *et al.* were immunoprecipitation and gel electrophoresis, which would be sufficient as a screening method as claimed. However, Kazlauskas *et al.* fail to explicitly teach such a use and the specific PDGF receptor sequences in the claims, SEQ ID NO: 2 and 4.

Sporn et al. teach that PDGF is "directly implicated" in, and consequently PDGF receptors are also directly implicated in, the involvement of several types of cancers (p. 330: column 1, paragraph 4). PDGF and PDGF receptors also play an important role in

tissue repair by acting as a potent chemoattractant for fibroblasts (p. 330: column 2, paragraph 3). Furthermore, Sporn *et al.* teach that growth factor antagonists present a viable approach in the treatment of disease (p. 331: column 2, paragraph 3).

Matsui *et al.* teach a PDGF receptor sequence that is 100% identical to SEQ ID NO: 2 (see figure 1 and sequence alignment: us-10-027-400-2.rup) and Gronwald *et al.* teach a PDGF receptor sequence that is 99.9% identical to SEQ ID NO: 4 (see figure 2 and sequence alignment: us-10-027-400-4.rup). Even though the sequence taught by Gronwald *et al.* is not 100% identical to SEQ ID NO: 4, it is identical enough so as to not make the sequence or the method of using the sequence novel. The only difference is at position 241 where an aspartic acid residue is replaced with a glutamic acid residue. This amino acid substitution would be considered conservative in nature since the amino acids are both classified as acidic amino acids and only differ by a methlyene group (CH_2). Furthermore, the claims drawn to methods of using SEQ ID NO: 4 do not claim the use of sequences comprising position 241 (see claims 46-49).

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Kazlauskas *et al.* and Sporn *et al.* to screen for compounds that inhibit the binding between a PDGF receptor and PI-3 kinase using the PDGF receptor sequences taught by Matsui *et al.* and Gronwald *et al.* A person of ordinary skill in the art would have been motivated to combine the teachings because Kazlauskas *et al.* provide a method useful for screening compounds that inhibit the binding between PDGF receptors and PI-3 kinase and Sporn *et al.* teach PDGF is involved in various types of cancers and antagonists are viable options in fighting

disease. Furthermore, the expectation of success would be reasonably assured because molecular biology techniques used by Kazlauskas *et al.* are standard techniques with high reproducibility. The instant invention is directed to a method of screening for compounds or molecules that inhibit the binding between a PDGF receptor and PI-3 kinase. The method taught by Kazlauskas *et al.* discloses the same method, in that it is able to detect association between PDGF receptors and cellular proteins, one of which is an 84 kD protein presumed to be PI-3 kinase in the absence of any evidence to the contrary, and PI-3 kinase activity, as noted above. The method taught by Kazlauskas *et al.* would be able to be utilized in the context of the present invention as follows:

1. Stimulate PDGF receptors and detect cellular changes, *e.g.* receptor phosphorylation dependent association. Results from the first step would represent control values.

2. Stimulate PDGF receptors in the presence of an unknown and detect cellular changes, *e.g.* receptor phosphorylation dependent association. Results from the second step can be used to compare results of the first step indicating the ability of the unknown to inhibit binding of the polypeptides.

In order to fully address Applicant's arguments and for the sake of compact prosecution, arguments set forth in response to the previous 35 U.S.C. § 103(a) rejection citing Kazlauskas *et al.* and Sporn *et al.* in the office action of 15 November 2004 are addressed.

Applicant argues that Kazlauskas *et al.* teach autophosphorylation of Tyr-751 is responsible for the interaction with cell proteins and PI-3 kinase activity. Furthermore, Applicant argues there is nothing to suggest the instant method of screening, whereby PDGF receptors and PI-3 kinase interact as a result of at least one phosphorylated tyrosine at position 708 and 719. Applicant states that "extensive research" has been done to investigate the interaction between PDGF receptors and PI-3 kinase. Applicant also argues the teachings by Sporn *et al.* concerning the involvement of PDGF in cancer has nothing to do with the screening method claimed. Finally, Applicant argues the rejection is based on hindsight reasoning and there is nothing to suggest the instant screening method.

It is duly noted that Kazlauskas *et al.* do not teach that Tyr-708 or Tyr-719 are at least partly responsible for mediating interactions between PDGF receptors and PI-3 kinase. Applicant's findings have scientific merit, however they do not impart patentability in the instant invention. Just because Applicant performed "extensive research" to elucidate specific autophosphorylation sites that are involved in docking of PI-3 kinase does not mean the invention is patentable. The teachings by Kazlauskas *et al.* indicate, as previously noted, that PI-3 kinase binds to PDGF receptors upon activation of the receptor, *i.e.* association of an 84 kD protein, and result in increased PI-3 kinase activity (p. 1129: column 2, paragraph 2). Again, Applicant's finding are interesting research finding, but do not represent a patentable invention because it was known in the art a the time of the invention that PDGF receptors associate with PI-3 kinase and induces PI-3 kinase activity and that PDGF and PDGF receptors are

involved in disease. Therefore it would have been obvious to develop a method of screening molecules that inhibit the binding between PDGF receptors and PI-3 kinase, particularly using the kinase insert region, which includes Tyr-751 as taught by Kazauskas *et al.*, to develop antagonist directed to PDGF receptors in an effort to alleviate diseases associated with PDGF/PDGF receptors. Furthermore, autophosphorylation is an event that occurs upon receptor activation, thus phosphorylation of at least Tyr-719, an autophosphorylation site in the kinase insert region, would have inherently occurred regardless of whether this phenomenon was recognized or not (Escobedo *et al.*, Mol Cell Biol. 1991, Vol. 11(2): pp. 1125-1132, esp. p. 1125: column 1, paragraph 1).

In regards to the teachings cited by Sporn *et al.* and Applicant's assertion that these teachings have nothing to do with the instant invention, it appears that Applicant has misunderstood the relevance and significance of what was taught. It was clearly set forth in the 35 U.S.C. § 103(a) rejection in the office action of 15 November 2004 that Sporn *et al.* teach, "PDGF is "directly implicated" in, and consequently PDGF receptors are also directly implicated in, the involvement of several types of cancers". Sporn *et al.* provide motivation to develop the method as a result of the findings and methods taught by Kazauskas *et al.*

Conclusion

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **J. Jason Galvez, Ph.D**. whose telephone number is **571-272-2935**. The examiner can normally be reached Monday through Friday 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback, Ph.D.** can be reached at **571-272-0887**.

The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JJG
4/11/2005

JANET ANDRES
PRIMARY EXAMINER